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cont composition of claim ~~46~~³⁸ is from about 0.01 mg/kg/day to about 300 mg/kg/day.

Please add claim 58.

A7 ⁴⁹58. The method of claim ~~46~~³⁸ wherein the integrin mediated disorder is a cell-proliferative disorders.

REMARKS/ARGUMENTS

The present application is subject to a restriction requirement under 35 USC 121 between:

Group (I), Claims 1-57 drawn to compounds of formula (I) where B₂ represents C₁ alkylene or C₁ alkenylene and B₁ represents C₁₋₂ alkylene or C₁₋₂ alkenylene, pharmaceutical compositions containing these compounds and methods of using these compounds classified in class 546; and

Group (II), Claims 1-23, 25-27 and 32-57, drawn to compounds of formula (I) where b and B are other than defined above for Group I.

Applicants respectfully affirm the election of Group I with traverse.

From a brief review of the classification system Applicants understand Class 546 to include 6 membered ring structures having one heteroatom (i.e. N). Therefore, it would appear that B₁ and B₂ both C₁₋₂ alkylene or alkenylene groups and satisfy the requirements of Class 546. Accordingly, compounds where B₁ and B₂ both C₁₋₂ alkylene or alkenylene groups could be searched concurrently with no additional burden. Therefore, applicants object to the restriction requirement between Group I and Group II as currently defined and request the scope Group I of the Restriction Requirement be modified.

Claims 1-19, 21-36, 44-46 and 48-57 remain in this application. Claims 20, 37-43 and 47 are being canceled. Claims 1, 25, 26, 45, 48, 50-53, 55, and 56 have been amended. Claim 58 has been added.

Claims 1, 25, and 26 have been amended to expedite prosecution of the present application. Support for this amendment exists in the specification and within claim 21. Claim 45 has been amended from a product-by-process claim to a

method claim. Claim 48 has been amended to change the dependency to 46 from canceled claim 47. Claims 50, 52, 53, 55 and 56 have been amended to correct various informalities. Claim 51 was amended and claim 58 has been added as a result of the separating the members of the Markush group from claim 50. Applicants, therefore, respectfully submit that the amendments to claims 1, 25, 26, 45, 48, 50-53, 55, and 56 and new claim 58 do not add new matter and request entry of these amendments and claims to further prosecution of this patent application.

By these amendments, the Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which the Applicants are entitled. The cancellation of claims 20, 37-43 and 47 as well as the amendments to claims 1, 25, 26, 45, 48, 50-53, 55 and 56 have been made solely to promote the progress of the instant application.

The rejection of claims 1, 24, 25, and 26 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because "racemic mixtures, diastereomers and enantiomers thereof" was indefinite and there is no teaching on how to make these compounds.

Applicants respectfully submit that those of ordinary skill in the art are well aware of what these terms mean and how to synthesis racemic mixtures and resolve diastereomers. On page 22 of the application beginning on line 19 and continuing page 23, line 8 applicants have described racemic mixtures, enantiomers and diastereomers compounds of the present invention. Accordingly, applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph of claims 1, 24, 25 and 26.

The rejection of claims 37-43 under 35 U.S.C. §112, second paragraph, as being a duplication of claims 46-51 was reviewed.

Since no loss of scope is involved in the canceling of claims 37-43 and retaining claims 46-51, to expedite prosecution applicants have canceled claims 37-43.

The rejection of claim 45 under 35 U.S.C. §112, second paragraph, as being a duplicate of claim 44 was reviewed. However, since claim 44 is directed a composition and the claim 45 as amended is directed to a method of making a composition applicants respectfully request withdrawal of the rejection of claim 45.

The rejections under 35 U.S.C. §112, second paragraph, of claims 50-53, 55, and 56 have been reviewed. However in view of the amendments to these claims the applicants respectfully submit that the rejection of these claims are no longer appropriate. Claims 50 and 51 have been amended to avoid overlap within the claims. Claims 52 and 53 have been amended to be method rather than composition claims. Claims 55 and 56 have been amended to be method of treatment claims consistent with claim 46. Accordingly, applicants request reconsideration of these claims.

None of the amendments made herein are intended to limit the scope of the claims and do not imply that applicants have surrender any of the subject matter or equivalents of the subject matter present in these claims.

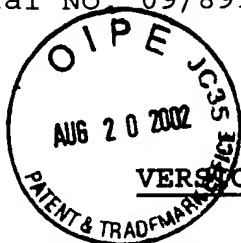
Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page(s) is/are captioned "Version with markings to show changes made".

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

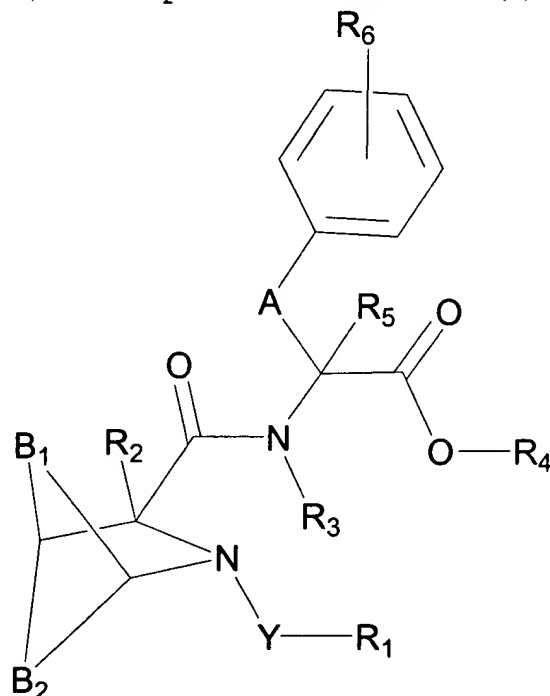
Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

2. (Once Amended) A compound of Formula (I):



Formula (I)

wherein

Y is selected from the group consisting of a bond, -C(O)-, -C(O)O-, -C(O)NH- and -SO₂-;

R₁ is selected from the group consisting of R₇ and R₈;

R₂, R₃, R₄ and R₅ are independently selected from the group consisting of a bond, hydrogen and C₁₋₈alkyl; wherein C₁₋₈alkyl is optionally substituted with one to three substituents independently selected from R₉, provided that R₂, R₃, R₄ or R₅ can only be a bond when forming a monocyclic ring wherein the following monocyclic rings may be formed from R₂, R₃, R₄ and R₅;

when R₂ and R₃ comprise a bond and C₁₋₈alkyl or optionally when both R₂ and R₃ are C₁₋₈alkyl, R₂ and R₃ together with the atoms to which each is attached will form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R₃ and R₄ comprise a bond and C₁₋₈alkyl or optionally when both R₃ and R₄ are C₁₋₈alkyl, R₃ and R₄ together with the atoms to which each is attached will form a five to seven membered monocyclic ring optionally containing one

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to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_3 and R_5 comprise a bond and C_{1-8} alkyl or optionally when both R_3 and R_5 are C_{1-8} alkyl, R_3 and R_5 together with the atoms to which each is attached will form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_4 and R_5 comprise a bond and C_{1-8} alkyl, or optionally when both R_4 and R_5 are C_{1-8} alkyl, R_4 and R_5 together with the atoms to which each is attached will form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

R_6 is optionally present and is one to three substituents independently selected from the group consisting of halogen, C_{1-8} alkoxy, R_{10} , R_{12} , $-N(R_{11})C(O)-R_{10}$, $-N(R_{11})C(O)-R_{12}$, $-N(R_{11})SO_2-R_{10}$, $-N(R_{11})SO_2-R_{12}$, $-N(R_{11})C(O)-N(R_{11},R_{10})$, $-N(R_{11})C(O)-N(R_{11},R_{12})$, $-N(R_{11})C(O)-N(R_{12},R_{17})$, $-C(O)-N(R_{11},R_{10})$, $-C(O)-N(R_{11},R_{12})$, $-C(O)-N(R_{12},R_{17})$, $-OC(O)-N(R_{11},R_{10})$, $-OC(O)-N(R_{11},R_{12})$, $-OC(O)-N(R_{12},R_{17})$, $-OC(O)-R_{10}$, $-OC(O)-R_{12}$, $-O-R_{10}$ and $R_{10}-(C_{1-8})$ alkoxy;

R_7 , R_9 , R_{10} and R_{14} are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, $N-(C_{1-8}$ alkyl)amino, $N,N-(C_{1-8}$ dialkyl)amino, $-CF_3$ and $-OCF_3$; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three oxo substituents; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, $N-(C_{1-8}$ alkyl)amino, $N,N-(C_{1-8}$ dialkyl)amino, $-CF_3$ and $-OCF_3$;

R_8 , R_{12} , R_{13} and R_{17} are independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and $(halo)_{1-3}(C_{1-8})$ alkyl; wherein C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted on a terminal carbon with one to three substituents independently selected from R_{14} ;

R₁₁ is selected from the group consisting of hydrogen and C₁₋₈alkyl;

A is C₁₋₄alkylene optionally substituted with one to two substituents independently selected from R₁₃;

when R₃ is C₁₋₈alkyl, optionally A and R₃ together with the atoms to which each is attached may form a five to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

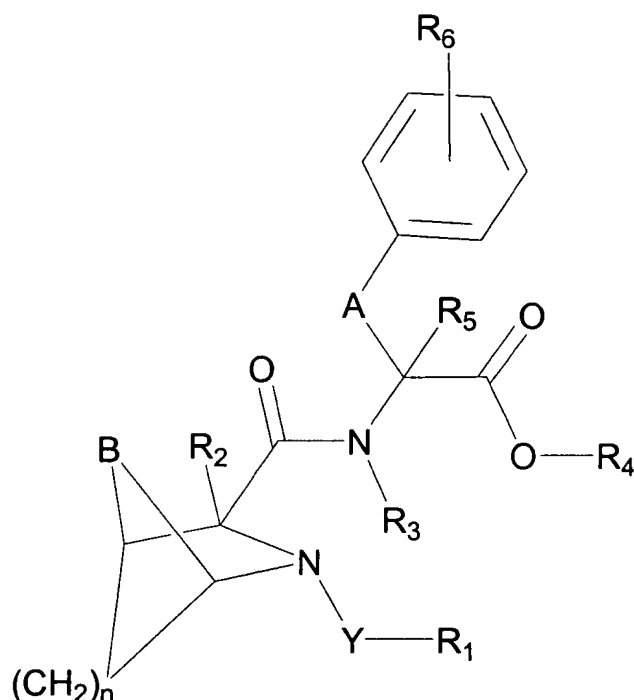
when R₄ is C₁₋₈alkyl, optionally A and R₄ together with the atoms which each is attached may form a five to seven membered monocyclic ring optionally containing one additional heteroatom selected from the group consisting of N, O and S;

when R₅ is C₁₋₈alkyl, optionally A and R₅ together with the atoms which each is attached may form a three to seven membered monocyclic ring optionally containing one to two heteroatoms independently selected from the group consisting of N, O and S; and,

B₁ and B₂ are independently selected from the group consisting of C₁₋₂alkylene and C₂alkenylene [C₁₋₈alkylene and C₂₋₈alkenylene] optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, carboxyl, amino, N-(C₁₋₈alkyl)amino, N,N-(C₁₋₈dialkyl)amino, -CF₃ and -OCF₃;

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof.

25. (Once Amended) A compound having Formula (II):



Formula (II)

wherein

Y is selected from the group consisting of $-C(O)-$ and $-SO_2-$;

R_1 is selected from the group consisting of R_7 and R_8 ;

R_2 , R_3 , R_4 and R_5 are independently selected from the group consisting of a bond, hydrogen and C_{1-8} alkyl; wherein C_{1-8} alkyl is optionally substituted with one to three substituents independently selected from R_9 ; provided that R_2 , R_3 , R_4 and R_5 can only be a bond when forming a monocyclic ring wherein the following monocyclic rings may be formed from R_2 , R_3 , R_4 and R_5 :

when R_2 and R_3 comprise a bond and C_{1-8} alkyl or optionally when both R_2 and R_3 are C_{1-8} alkyl, R_2 and R_3 together with the atoms to which each are attached form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_3 and R_4 comprise a bond and C_{1-8} alkyl or optionally when both R_3 and R_4 are C_{1-8} alkyl, R_3 and R_4 together with the atoms to which each are attached form a five to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_3 and R_5 comprise a bond and C_{1-8} alkyl or optionally when both R_3 and R_5 are C_{1-8} alkyl, R_3 and R_5 together with the atoms to which each are attached form a four to seven

membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R_4 and R_5 comprise a bond and C_{1-8} alkyl or optionally when both R_4 and R_5 are C_{1-8} alkyl, R_4 and R_5 together with the atoms to which each are attached form a four to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

R_6 is optionally present and is one to three substituents independently selected from the group consisting of halogen, C_{1-8} alkoxy, R_{10} , R_{12} , $-N(R_{11})C(O)-R_{10}$, $-N(R_{11})C(O)-R_{12}$, $-N(R_{11})SO_2-R_{10}$, $-N(R_{11})SO_2-R_{12}$, $-N(R_{11})C(O)-N(R_{11}, R_{10})$, $-N(R_{11})C(O)-N(R_{11}, R_{12})$, $-N(R_{11})C(O)-N(R_{12}, R_{17})$, $-C(O)-N(R_{11}, R_{10})$, $-C(O)-N(R_{11}, R_{12})$, $-C(O)-N(R_{12}, R_{17})$, $-OC(O)-N(R_{11}, R_{10})$, $-OC(O)-N(R_{11}, R_{12})$, $-OC(O)-N(R_{12}, R_{17})$, $-OC(O)-R_{10}$, $-OC(O)-R_{12}$, $-O-R_{10}$ and $R_{10}-(C_{1-8})$ alkoxy;

R_7 , R_9 , R_{10} and R_{14} are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, $N-(C_{1-8})$ alkylamino, $N,N-(C_{1-8})$ dialkylamino, $-CF_3$ and $-OCF_3$; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three oxo substituents; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, $N-(C_{1-8})$ alkylamino, $N,N-(C_{1-8})$ dialkylamino, $-CF_3$ and $-OCF_3$;

R_8 , R_{12} , R_{13} and R_{17} are independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and $(halo)_{1-3}(C_{1-8})$ alkyl; wherein C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted on a terminal carbon with one to three substituents independently selected from R_{14} ;

R_{11} is selected from the group consisting of hydrogen and C_{1-8} alkyl;

A is C_{1-4} alkylene optionally substituted with one to two substituents independently selected from R_{13} ;

when R₃ is C₁₋₈alkyl, optionally A and R₃ together with the atoms to which each is attached form a five to seven membered monocyclic ring optionally containing one to two additional heteroatoms independently selected from the group consisting of N, O and S;

when R₄ is C₁₋₈alkyl, optionally A and R₄ together with the atoms to which each is attached form a five to seven membered monocyclic ring optionally containing one additional heteroatom selected from the group consisting of N, O and S;

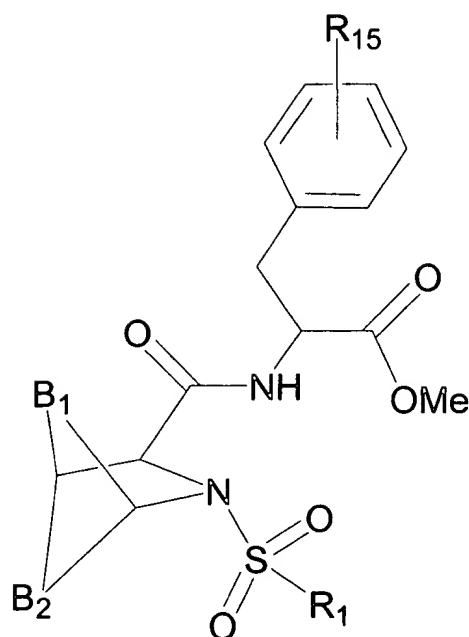
when R₅ is C₁₋₈alkyl, optionally A and R₃ together with the atoms to which each is attached form a three to seven membered monocyclic ring optionally containing one to two heteroatoms independently selected from the group consisting of N, O and S;

B is selected from the group consisting of C₁₋₂alkylene and C₂alkenylene [C₁₋₈alkylene and C₂₋₈alkenylene] optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, carboxyl, amino, N-(C₁₋₈alkyl)amino, N,N-(C₁₋₈dialkyl)amino, -CF₃ and -OCF₃; and,

n is an integer from 1 to 2;

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof.

26. (Once Amended) A process for preparing a compound of Formula (III):



Formula (III)

wherein

R_1 is selected from the group consisting of R_7 and R_8 ;

R_7 , R_{10} , and R_{14} are independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylcarbonyl, C_{1-8} alkoxycarbonyl, carboxyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulfonyl, amino, N -(C_{1-8} alkyl)amino, N,N -(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$; wherein cycloalkyl and heterocyclyl are optionally substituted with one to three oxo substituents; and, wherein the aryl and heteroaryl substituents and the aryl portion of the arylcarbonyl substituent are optionally substituted with one to five substituents independently selected from the group consisting of halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, N -(C_{1-8} alkyl)amino, N,N -(C_{1-8} dialkyl)amino, $-CF_3$ and $-OCF_3$;

R_8 , R_{12} and R_{17} are independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and (halo) $_{1-3}$ (C_{1-8})alkyl; wherein C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted on a terminal carbon with one to three substituents independently selected from R_{14} ;

R_{15} is selected from the group consisting of hydroxy, amino, NO_2 and R_6 ;

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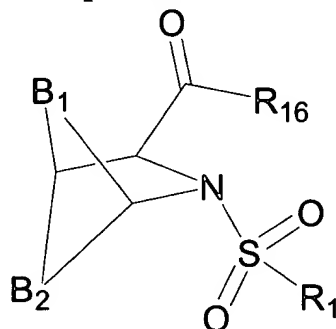
R_6 is optionally present and is one to three substituents independently selected from the group consisting of halogen, C_{1-8} alkoxy, R_{10} , R_{12} , $-N(R_{11})C(O)-R_{10}$, $-N(R_{11})C(O)-R_{12}$, $-N(R_{11})SO_2-R_{10}$, $-N(R_{11})SO_2-R_{12}$, $-N(R_{11})C(O)-N(R_{11},R_{10})$, $-N(R_{11})C(O)-N(R_{11},R_{12})$, $-N(R_{11})C(O)-N(R_{12},R_{17})$, $-C(O)-N(R_{11},R_{10})$, $-C(O)-N(R_{12},R_{17})$, $-C(O)-N(R_{11},R_{12})$, $-OC(O)-N(R_{11},R_{10})$, $-OC(O)-N(R_{11},R_{12})$, $-OC(O)-N(R_{12},R_{17})$, $-OC(O)-R_{10}$, $-OC(O)-R_{12}$, $-O-R_{10}$ and $R_{10}-(C_{1-8})$ alkoxy;

R_{11} is selected from the group consisting of hydrogen and C_{1-8} alkyl; and,

B_1 and B_2 are independently selected from the group consisting of C_{1-2} alkylene and C_{2-8} alkenylene [C_{1-8} alkylene and C_{2-8} alkenylene] optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, hydroxy(C_{1-8})alkyl, hydroxy(C_{1-8})alkoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, carboxyl, amino, $N-(C_{1-8}alkyl)amino$, $N,N-(C_{1-8}dialkyl)amino$, $-CF_3$ and $-OCF_3$;

and pharmaceutically acceptable salts, racemic mixtures, diastereomers and enantiomers thereof;

comprising reacting a compound of Formula (IV)

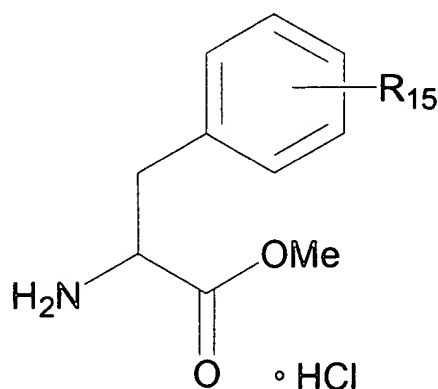


Formula (IV)

wherein

R_{16} is selected from the group consisting of halogen, mixed anhydride and hydroxy;

with a compound of Formula (V)



Formula (V);

in the presence of appropriate coupling agents, bases and solvents to form the compound of Formula (II).

45 (Once Amended) A method of making a pharmaceutical composition [made by] comprising mixing a compound of claim 1 and a pharmaceutically acceptable carrier.

48. (Once Amended) The method of claim 46 [47] wherein the $\alpha 4$ integrin receptor is selected from the group consisting of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin receptor.

50. (Once Amended) The method of claim 46 wherein the integrin mediated disorder is [selected from the group consisting of] a inflammatory disorders[, autoimmune disorders and cell-proliferative disorders].

51. (Once Amended) The method of claim 46 wherein the integrin mediated disorder is [selected from the group consisting of inflammation disorders,] autoimmune disorders[, asthma, bronchoconstriction, restenosis, atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, irritable bowel disease, irritable bowel syndrome, transplant rejection and multiple sclerosis].

52. (Once Amended) The method [compound] of claim 46 wherein the integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, irritable bowel disease, irritable bowel syndrome, transplant rejection and multiple sclerosis.

53. (Once Amended) The method [compound] of claim 46 wherein the integrin mediated disorder is selected from the group consisting of asthma, bronchoconstriction, restenosis, atherosclerosis, irritable bowel syndrome and multiple sclerosis.

55. (Once Amended) The method of claim 46 further comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of claim 46 [44] combined with a pharmaceutically acceptable carrier.

56. (Once Amended) The method of claim 55 wherein the therapeutically effective amount of the pharmaceutical composition of claim 46 [44] is from about 0.01 mg/kg/day to about 300 mg/kg/day.

Please add claim 58.

58. The method of claim 46 wherein the integrin mediated disorder is a cell-proliferative disorders].